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Room 6-71
5600 Fishers Lane
Rockville, MD 20857

Re: Petitions for Stay of Action Regarding Effective Approval of Any ANDA for a Generic Version of Platinol®-AQ
FDA Docket No. 99P-1271

Dear Ms. Dickinson:

We are submitting this letter on behalf of Pharmachemie B.V. ("Pharmachemie") to reply to the arguments advanced in Leydig, Voit & Mayer, Ltd.'s letter of June 18, 1999 on behalf of American Pharmaceutical Partners, Inc. ("APP") regarding the two pending Petitions for Stay of Action that address rights to the 180-day delay period for generic versions of Platinol®-AQ (cisplatin injection). APP's arguments are fundamentally flawed. As explained below, those arguments rely on inaccurate interpretations of the relevant regulations and recent court actions and are completely at odds with § 505(j)(5)(B)(iv) of the Food, Drug, and Cosmetic Act ("FDCA"), which creates the 180-day delay period.

21 C.F.R. § 314.107(c)(1) Does Not Provide Any Basis to Delay Approval of Pharmachemie's ANDA

APP's position that it is entitled to exclusivity is premised on its invocation of 21 C.F.R. § 314.107(c) (1), which provides as follows:

> *Subsequent abbreviated new drug application submission.* (1) If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that the same patent was invalid, unenforceable, or would not be infringed [and the applicant submitting the first application has successfully defended against a suit for patent infringement brought within 45 days of the patent owner's receipt

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> of notice submitted under § 314.95],[1] approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier. . .

As indicated by its title, this subsection refers to a "subsequent abbreviated new drug application submission" and the conditions under which effective approval of such a subsequent ANDA will be deferred for 180 days. The operative language of the regulation makes clear that it only applies to a subsequent ANDA – "approval of the subsequent abbreviated new drug application will be made effective no sooner than 180 days from whichever of the following dates is earlier. . . ." Pharmachemie's ANDA for a generic version of Platinol®-AQ containing a Paragraph IV certification was accepted for filing by FDA on May 26, 1995. The ANDA now being pursued by APP was not, according to APP, filed until August 24, 1995. Pharmachemie's ANDA was not subsequent to the APP ANDA and therefore 21 C.F.R. § 314.107(c)(1) cannot provide a basis for delaying approval of Pharmachemie's ANDA for 180 days. APP ignores the clear language in the regulation that limits its application to a "subsequent abbreviated new drug application."

Furthermore, APP's assertion that this regulation entitles it to a 180-day period of exclusivity over Pharmachemie's previously submitted ANDA is completely at odds with the statute. Section 505(j)(5)(B)(iv) of the FDCA makes clear that the first applicant to file an ANDA with a Paragraph IV certification is entitled to the benefit of the 180-day delay period. That section provides:

> If the application contains a certification described in subclause IV of paragraph (2)(A)(viii) and is for a drug *for which a previous application* has been submitted under the subsection containing such a certification, the application shall be made effective not earlier than 180 days after . . . . (emphasis added)

APP's ANDA is not "previous" to Pharmachemie's ANDA, and therefore can provide no basis for delaying approval of Pharmachemie's ANDA under this provision.

APP's reading of the statute and 21 C.F.R. 314.107(c), carried to its logical conclusion, suggests that each patent on a drug creates a separate entitlement to a 180-day delay period, which could well lead to multiple 180-day delay periods for a single drug. FDA has never read the statute to allow multiple delay periods, and it should not do so now. Allowing multiple delay periods would be almost impossible to administer, create chaos in the marketplace, and further delay generic competition. Indeed, if the priority order of Paragraph IV applicants for purposes of the 180-day delay clause were determined patent by patent, it

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1. As you know, the bracketed portion was invalidated by *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998).

could lead to a situation where generic competition was prevented altogether by different applicants' entitlements to mutually blocking 180-day delay periods - plainly an absurd result.

Pharmachemie's Statutory Entitlement to the Benefit of the 180-Day Delay Period is Not Affected by Either the Expiration of the '515 Patent or the Fact that Pharmachemie's Amended Certification with Respect to the '925 Patent Occurred After the APP Certification on that Patent

APP's argument that Pharmachemie is not entitled to the benefit of the 180-day delay because of the expiration of the '515 patent also fails. The fact that the '515 patent, to which Pharmachemie's original Paragraph IV certification was addressed, has since expired is irrelevant, and APP provides no citation to the governing statute or applicable regulations to support its argument on this issue. In fact, as quoted above, the statute expressly provides that the first applicant to submit an ANDA with a Paragraph IV certification and to continue the certification is entitled to the benefit of the 180-day delay period. The statute makes no provision for removing that entitlement when a patent expires. FDA is not authorized to alter the terms of the statute by taking away something, here the benefit of the 180-day delay period, that Congress expressly created.[2] *See Mova v. Shalala*, 140 F.3d at 1069; *Granutec, Inc. v. Shalala*, Nos. 97-1873, 1874, 1998 U.S. App. LEXIS 6685, at *21 (4th Cir. May 7, 1998) (per curiam) (striking down "successful defense" portion of 21 C.F.R. § 314.107(c)(1)).

Moreover, even if Pharmachemie were not entitled to the benefit of the 180-day delay period solely on the basis of its Paragraph IV certification with respect to the '515 patent, it also has a Paragraph IV certification on the '925 patent. The fact that Pharmachemie added the Paragraph IV certification with respect to the '925 patent subsequent to its initial filing of the ANDA and after APP's certification with respect to the '925 patent does not affect its entitlement to the statutory 180-day delay period. The statute provides that subsequent Paragraph IV ANDAs are subject to the 180-day delay in approval if there is a prior ANDA

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2. APP argues that, if and when its Paragraph IV certification to the '515 patent is amended to a Paragraph II certification, that certification will no longer count for purposes of the 180-day delay clause. Pharmachemie notes that FDA has already rejected this view in the context of tamoxifen (Docket No. 98P-0493), although Pharmachemie is currently opposing FDA's position on this issue in *Pharmachemie v. Henney*, No. 99CV801 (D.D.C.). Pharmachemie also notes that, in contrast to the applicant that was first to file a Paragraph IV certification in the tamoxifen case (Barr Laboratories), here Pharmachemie is actively pursuing effective approval of its ANDA with the intention of expediting market entry of generic cisplatin, as the Hatch-Waxman statute contemplates.

that contains a Paragraph IV certification. There is no question that Pharmachemie's ANDA was filed prior to APP's ANDA and that Pharmachemie's ANDA has contained a Paragraph IV certification since it was submitted.[3]

The statute does not make a distinction in application of this delay in approval with respect to different patents as to which certification may be made. APP's citation of the portion of the statute requiring that "a certification . . . [be made] with respect to each patent which claims the listed drug" does not support APP's argument that the 180-day approval delay must be applied separately with respect to each patent as to which a certification is made. 21 U.S.C. § 355(j)(2)(A)(vii). In fact, Pharmachemie fully complied with the statutory provision, certifying as to the only patent in effect when it submitted its ANDA and continuing a Paragraph IV certification at all times.

APP's effort to distinguish the holding in *Granutec v. Shalala* (attached as part of Exhibit B to Pharmachemie's June 9, 1999 Petition for Stay) is unavailing. There were two separate patents involved in the three successive Paragraph IV certifications at issue there. The Fourth Circuit flatly rejected arguments that the first party to submit an ANDA with a Paragraph IV certification "lost its place in line as the first ANDA application" merely because it later amended its ANDA patent, first to add another Paragraph IV certification with respect to a second patent and then to cover a different form of the drug. The Fourth Circuit in *Granutec* held that the first party to file an ANDA with a Paragraph IV certification was entitled to the benefit of the 180-day delay period, despite the fact that the original certification did not cover the form of the drug ultimately sought to be marketed. The subsequent certifications were held to relate back to the date of the initial ANDA application. 1998 U.S. App. LEXIS 6685, at *21 n.1. Even to the extent that the successive certifications at issue in *Granutec* involved the same patent, APP's attempt to distinguish that case fails. The point of the Court's holding in *Granutec* is that the sequence of later Paragraph IV certifications cannot alter the priority order of Paragraph IV applications on a drug, which is established by the sequence of the initial ANDA filings with a Paragraph IV certification. Whether those later certifications are to the same or different patents is immaterial. Like the original applicant in the *Granutec* case, which repeatedly and significantly changed the nature of its Paragraph IV certification over time, Pharmachemie did not lose its place in line merely because it later added a Paragraph IV certification with respect to a second patent.

APP's position is not only wrong as a matter of statutory interpretation, it is inconsistent with the policy behind the Hatch-Waxman Act. At the time that Pharmachemie submitted its Paragraph IV ANDA for cisplatin, it was the first Paragraph IV filer for this drug. As such, Pharmachemie became entitled to the benefit of the 180-day delay provision,

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3. APP's tortured interpretation of 21 C.F.R. § 314.107(c)(1) is again unavailing. Even if APP removes its certification with respect to the '515 patent, both the APP and Pharmachemie ANDAs contain a certification that the same patent, the '925, is invalid and thus the regulation is satisfied. APP, as the subsequent applicant, is subject to the 180-day delay in approval.

which the agency has acknowledged was intended to reward the first applicant to take on the burden and risk of challenging the existing patent or patents on a drug. The fact that Bristol Myers Squibb subsequently obtained and listed another patent, as to which Pharmachemie filed its Paragraph IV certification subsequent to APP, is mere happenstance that cannot and should not affect Pharmachemie's position as the first Paragraph IV applicant for this drug. Indeed, were it not for the listing of this second patent, and the litigation and corresponding 30-month stay that stemmed from Pharmachemie's challenge to that patent, Pharmachemie would have received final approval from FDA, placed its generic cisplatin on the market and thus would already have enjoyed the benefit of the 180-day delay period. To now deprive Pharmachemie of that benefit because of the sequence of Paragraph IV filings on a subsequently listed patent would be to treat Pharmachemie's initial patent challenge as if it had never happened. Not only would such an approach be clearly contrary to reality and common sense, but it would undercut the fundamental purpose of the 180-day delay provision by making the first applicant's eligibility for the benefits of that provision vulnerable to the effects of unforeseeable chance occurrences (and possible manipulation by the brand drug company) later on - severely weakening the patent challenge incentive that the statute is intended to create.

As demonstrated above, the statutory language concerning the 180-day delay in approval for subsequent ANDAs establishes that Pharmachemie, as the first ANDA applicant with a Paragraph IV certification, is entitled to the benefit of this delay provision and that APP, as a subsequent applicant, should be subject to that statutorily-imposed delay. APP's efforts to turn the statute on its head should be rejected.

Lastly, a brief response to the June 17, 1999 letter to you from David Weeda of Olsson, Frank & Weeda, P.C., another law firm representing APP, concerning the topic of the relationship between the patent case involving the '925 patent and the timing of FDA's decision on these issues. Mr. Weeda is correct to the extent that the presentation of evidence was completed in the patent case on June 15, 1999. The date for final argument, however, previously scheduled for July 22, 1999, has now been postponed by Judge Brown until July 28, 1999. Pharmachemie continues to believe that, as the record now stands, APP has represented to the Court in the patent case that it has no intention of marketing its generic cisplatin solution product, even if permitted to do so by FDA, until at least 30 days after July 28, 1999, to permit Judge Brown time to render his decision in that case.

Sincerely,

Kate Beardsley

Kate C. Beardsley

cc: Docket No. 99P-1271